

TENT COOPERATION TREATY

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RANBAXY
IP DEPARTMENT

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

To:
RANBAXY LABORATORIES LIMITED
Attn. Deshmukh, Jay R.
600 College Road East
Suite 2100
Princeton, NJ 08540
UNITED STATES OF AMERICA

(PCT Rule 44.1)

Applicant's or agent's file reference RLL-544WO	Date of mailing (day/month/year) 08/07/2005
International application No. PCT/IB2004/003893	International filing date (day/month/year) 26/11/2004
Applicant RANBAXY LABORATORIES LIMITED	

FOR FURTHER ACTION See paragraphs 1 and 4 below

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders


Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31.651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Federico Bonomelli
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MRL ✓

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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference RLL-544WO	FOR FURTHER ACTION <div style="text-align: right; font-size: small;">see Form PCT/ISA/220 as well as, where applicable, item 5 below.</div>	
International application No. PCT/IB2004/003893	International filing date (day/month/year) 26/11/2004	(Earliest) Priority Date (day/month/year) 26/11/2003
Applicant RANBAXY LABORATORIES LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box II).

3. ☒ **Unity of invention is lacking** (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

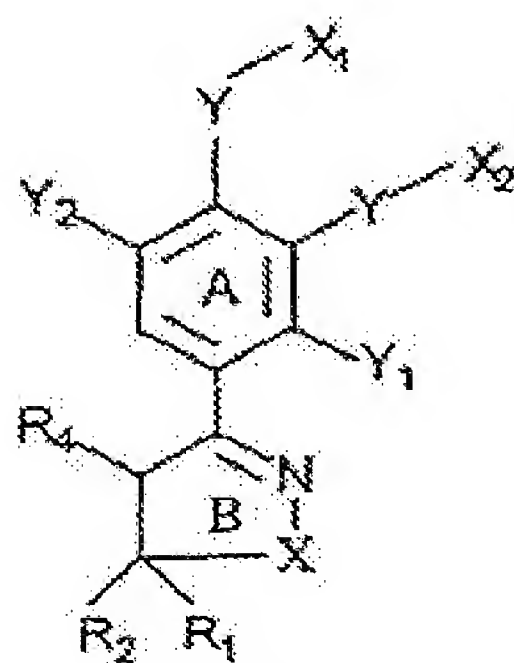
☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to isoxazoline derivatives of structure (I) and their analogues, which can be used as phosphodiesterase (PDE) type IV selective inhibitors. Compounds disclosed herein can be useful in the treatment of AIDS, asthma, arthritis, bronchitis, chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic dermatitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma, allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases especially in humans. Processes for the preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds, and their use as PDE type IV selective inhibitors, are provided.



Formula I

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D261/04 C07D413/04 C07D417/04 C07D413/14 C07D413/12
A61K31/42 A61K31/422

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 95/14680 A (PFIZER INC; KLEINMAN, EDWARD, F) 1 June 1995 (1995-06-01) cited in the application page 40, line 7; claim 1 page 21; example 28	1, 2, 5, 6, 8-13, 21
X	DE 199 09 785 A1 (BAYER AG) 7 September 2000 (2000-09-07) claim 1 example 1	1, 2, 6, 8-10

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search

1 June 2005

Date of mailing of the international search report

08.07.05

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kollmannsberger, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOLINA; C T; AGUIAR A P: "Synthesis of new 4,5-dihydroisoxazoles with potential anti-inflammatory activity" HETEROCYCLIC COMMUNICATIONS., vol. 9, no. 5, 2003, pages 535-538, XP009044208 FREUND PUBLISHING HOUSE, TEL AVIV. compound 6	1,2,5, 8-10
X	DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; RAI, K. M. LOKANATHA ET AL: "Intermolecular 1,3-dipolar cycloaddition of nitrile oxides with vinyl acetate and acrylonitrile" XP002318408 retrieved from STN Database accession no. 1997:323068 compounds with RN 190907-46-1, 190907-47-2, 190907-48-3 abstract & INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY, 36B(3), 242-245 CODEN: IJSBDB; ISSN: 0376-4699, 1997,	1,2,5
A	WO 95/14861 A (AOYAGI, SOICHIRO) 1 June 1995 (1995-06-01) cited in the application claims	1-28
X	FIHI R ET AL: "REACTION SES METHYLENE GAMMA-BUTYROLACTONES AVEC LES ARYLNITRILOXYDES. EVOLUTION INATTENDUE DU BISADDUIT ISSU DE LA 5-METHYLENE(5H)FURAN-2-ONE" BULLETIN DES SOCIETES CHIMIQUES BELGES, vol. 104, no. 1, 1995, pages 55-62, XP009044216 ISSN: 0037-9646 compounds 6F,8F	1,3,8
X	RAI K M L ET AL: "A CONVENIENT METHOD OF THE GNERATION OF NITRILE OXIDE AND ITS APPLICATION TO THE SYNTHESIS OF 2-ISOXAZOLINES" ORGANIC PREPARATIONS AND PROCEDURES INTERNATIONAL, ORGANIC PREPARATION AND PROCEDURES CO., NEWTON HIGHLANDS, MA, US, vol. 24, no. 1, 1992, pages 91-94, XP009044215 ISSN: 0030-4948 compounds 3A,3D	1,8

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>AL-TIMARI U A R ET AL: "REGIOSELECTIVE SYNTHESIS OF C-NUCLEOSIDES BY 1,3-DIPOLAR CYCLOADDITION OF ARYLNITRILE OXIDES TO 5,6-DIDEOXY-1,2-O-ISOPROPYLIDENE-ALPHA-D-XYL O-HEX-5-ENOFURANOSE"</p> <p>CARBOHYDRATE RESEARCH, ELSEVIER SCIENTIFIC PUBLISHING COMPANY, AMSTERDAM, NL, vol. 218, 1991, pages 121-127, XP009044213</p> <p>ISSN: 0008-6215</p> <p>compounds 3E, 3F, 4E, 4F</p>	1,3,8
X	<p>CLERICI FRANCESCA ET AL: "Isothiazole dioxides: synthesis and inhibition of Trypanosoma brucei protein farnesyltransferase."</p> <p>BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, 19 AUG 2002, vol. 12, no. 16, 19 August 2002 (2002-08-19), pages 2217-2220, XP002330201</p> <p>ISSN: 0960-894X</p> <p>table 1; compound 18</p>	1,3,8-12
X	<p>DATABASE CAPLUS 'Online!'</p> <p>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;</p> <p>HAFEZ, O. M. ABDEL ET AL: "New pyrazolines, isoxazolines and sulfides from 4,7-dimethoxy-5-acetyl-6-hydroxybenzofuran (Khellinone) and their antimicrobial activities"</p> <p>XP002330202</p> <p>retrieved from STN</p> <p>Database accession no. 1991:122152</p> <p>compound with RN 132600-64-7</p> <p>abstract</p> <p>& PAKISTAN JOURNAL OF SCIENTIFIC AND INDUSTRIAL RESEARCH, 33(5-6), 197-200</p> <p>CODEN: PSIRAA; ISSN: 0030-9885, 1990,</p>	1,3,7-12
X	<p>DATABASE CAPLUS 'Online!'</p> <p>CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US;</p> <p>KHALIL, ZARIF H. ET AL: "Synthesis and microbial activity of 5-heterocyclo-8-hydroxyquinolines"</p> <p>XP002330203</p> <p>retrieved from STN</p> <p>Database accession no. 1991:247104</p> <p>compound with RN 134145-31-6</p> <p>abstract</p> <p>& JOURNAL OF THE INDIAN CHEMICAL SOCIETY, 67(10), 821-3 CODEN: JICSAH; ISSN: 0019-4522, 1990,</p>	1,3,8-12

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOROLEVA, E. V. ET AL: "Cycloreversion of 5-(4-pyridyl)-2-isoxazolines in reactions with bases" XP002330204 retrieved from STN Database accession no. 1998:47410 compound with RN 202406-74-4 abstract & RUSSIAN JOURNAL OF ORGANIC CHEMISTRY (TRANSLATION OF ZHURNAL ORGANICHESKOI KHIMII), 33(1), 108-112 CODEN: RJOCEQ; ISSN: 1070-4280, 1997,</p>	1,3,8
A	<p>WO 02/081447 A (DAEWOONG PHARMACEUTICAL CO., LTD; PARK, JOON-SEOK; BYUN, YOUNG-SEOK; M) 17 October 2002 (2002-10-17) claims</p>	1-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/003893

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1 (part); 2,5,6; 8-12(part); 13,21

Compounds of structure (I) in which X=O and R2 is a linear substituent; compounds of structure (XXXIV); processes for their preparation and corresponding uses

2. claims: 1(part); 3,4; 8-12(part); 14-20, 22-28

Compounds of structure (I) in which X=O and R2 is a heterocyclic substituent; processes for their preparation and corresponding uses

3. claims: 1(part); 8-12(part)

Compounds of structure (I) in which X=S or NR8 and corresponding uses

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2004/003893

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9514680	A	01-06-1995	AT 187447 T	15-12-1999
			CA 2177375 A1	01-06-1995
			DE 69422061 D1	13-01-2000
			DE 69422061 T2	30-03-2000
			DK 730587 T3	10-04-2000
			EP 0730587 A1	11-09-1996
			ES 2139754 T3	16-02-2000
			FI 945556 A	27-05-1995
			GR 3032506 T3	31-05-2000
			WO 9514680 A1	01-06-1995
			JP 2818820 B2	30-10-1998
			JP 9500146 T	07-01-1997
			PT 730587 T	31-05-2000
			US 5686434 A	11-11-1997
DE 19909785	A1	07-09-2000	NONE	
WO 9514861	A	01-06-1995	JP 7145776 A	06-06-1995
			AU 7949894 A	13-06-1995
			WO 9514861 A1	01-06-1995
WO 02081447	A	17-10-2002	WO 02081447 A1	17-10-2002

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/B2004/003893

International filing date (day/month/year)
26.11.2004

Priority date (day/month/year)
26.11.2003

International Patent Classification (IPC) or both national classification and IPC
C07D261/04, C07D413/04, C07D417/04, C07D413/14, C07D413/12, A61K31/42, A61K31/422

Applicant
RANBAXY LABORATORIES LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

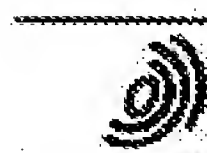
If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel: +49 89 2399-0 Tx: 523656 epmu d
Fax: +49 89 2399-4465

Authorized Officer:

Kollmannsberger, M
Telephone No. +49 89 2399-7364



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/003893

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☐ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/003893

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9-12

because:

☒ the said international application, or the said claims Nos. 9-12 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/003893

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	4,14-20,22-28
	No: Claims	1-3,5-13,21
Inventive step (IS)	Yes: Claims	4,14-20,22-28
	No: Claims	1-3,5-13,21
Industrial applicability (IA)	Yes: Claims	1-8,13-28
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 9-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

The present application deals with PDE-4 inhibitors and their corresponding uses. The claimed compounds share as a common structural feature an isoxazoline/isothiazoline/dihydropyrazole ring to which a substituted phenyl ring is attached. This structural feature, together with the use as PDE-4 inhibitors, could be regarded as a (corresponding) special technical feature that links the claimed compounds together to form a single general inventive concept in the sense of Rules 13.1. and 13.2. PCT. However, this concept is neither novel nor inventive since WO-A-9514680 (cited on page 2 of the description) discloses compounds (see examples) which act as PDE-4 inhibitors and show these structural features (it is noted that e. g. example 28 on page 21 of WO-A-9514680 is included in the scope of claim 1 for $R_2 = (CH_2)NHCOR_7$ and $R_7 = \text{alkyl}$ (substituted by halogen, cf. description page 7 line 5-7)). No other special technical feature is apparent which could link the claimed compounds together to form a single general inventive concept. The present application thus proposes to solve the problem of finding further PDE-4 inhibitors in three different, unrelated ways:

invention 1: claims 1 (part); 2,5,6; 8-12(part); 13,21

Compounds of structure (I) in which $X=O$ and R_2 is a linear substituent, compounds of structure (XXXIV); processes for their preparation and corresponding uses

invention 2: claims 1 (part); 3,4; 8-12(part); 14-20, 22-28

- CHIMIQUES BELGES, vol. 104, no. 1, 1995, pages 55-62, XP009044216 ISSN: 0037-9646
- D7: RAI K M L ET AL: "A CONVENIENT METHOD OF THE GNERATION OF NITRILE OXIDE AND ITS APPLICATION TO THE SYNTHESIS OF 2-ISOXAZOLINES" ORGANIC PREPARATIONS AND PROCEDURES INTERNATIONAL, ORGANIC PREPARATION AND PROCEDURES CO., NEWTON HIGHLANDS, MA, US, vol. 24, no. 1, 1992, pages 91-94, XP009044215 ISSN: 0030-4948
- D8: AL-TIMARI U A R ET AL: "REGIOSELECTIVE SYNTHESIS OF C-NUCLEOSIDES BY 1,3-DIPOLAR CYCLOADDITION OF ARYLNITRILE OXIDES TO 5,6-DIDEOXY-1,2-O-ISOPROPYLIDENE-ALPHA-D-X YL O-HEX-5-ENOFURANOSE" CARBOHYDRATE RESEARCH, ELSEVIER SCIENTIFIC PUBLISHING COMPANY. AMSTERDAM, NL, vol. 218, 1991, pages 121-127, XP009044213 ISSN: 0008-6215
- D9: CLERICI FRANCESCA ET AL: "Isothiazole dioxides: synthesis and inhibition of Trypanosoma brucei protein farnesyltransferase." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS. 19 AUG 2002, vol. 12, no. 16, 19 August 2002 (2002-08-19), pages 2217-2220, XP002330201 ISSN: 0960-894X
- D10: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HAFEZ, O. M. ABDEL ET AL: "New pyrazolines, isoxazolines and sulfides from 4,7-dimethoxy-5- acetyl-6-hydroxybenzofuran (Khellinone) and their antimicrobial activities" XP002330202 retrieved from STN Database accession no. 1991:122152
- D11: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KHALIL, ZARIF H. ET AL: "Synthesis and microbial activity of 5-heterocyclo-8- hydroxyquinolines" XP002330203 retrieved from STN Database accession no. 1991:247104
- D12: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOROLEVA, E. V. ET AL: "Cycloreversion of 5-(4-pyridyl)-2-isoxazolines in reactions with bases" XP002330204 retrieved from STN Database accession no. 1998:47410
- D13: WO 02/081447 A (DAEWOONG PHARMACEUTICAL CO., LTD; PARK, JOON-SEOK; BYUN, YOUNG-SEOK; M) 17 October 2002 (2002-10-17)

V.-2 Novelty (Art. 33(2) PCT):

ad invention 1:

D1 discloses compounds (see claim 1 for $R5=(CH_2)_nNHC(=O)X1$ and example 28 on page 21) included in the present claims. Since the compounds of D1 are disclosed as PDE-IV inhibitors, also the corresponding use claims are not novel.

D2-D4 disclose compounds included in the scope of claims 1,2,5,6,8-10 (see passages indicated in the search report).

Art. 33(2) PCT is not fulfilled.

ad invention 2:

The claims are novel over D1 because in D1 none of the substituents corresponding to R2 in the present claims can be a heterocycle. The same holds for D2-D5.

D6-D12 disclose compounds included in the scope of present claims 1, 3, 4 and 7 (see passages indicated in the search report). Since partly also medical uses as claimed in claims 8-12 are disclosed, also claims 8-12 are not novel. Claims 14-20,22-28 are not affected because the compounds to which these preparation processes lead are not disclosed in the cited documents.

ad invention 3:

None of the cited documents discloses compounds in which ring "B" is a thiazolidine or a dihydropyrazole. D13 discloses condensed systems (see claims). The parts of the claims relating to invention 3 are thus novel.

V-3. Inventive step (Art. 33(3) PCT).

ad invention 1:

The present application deals with PDE-IV inhibitors. Since compounds included in the present claims are known to be PDE-IV inhibitors from D1, the problem of finding further PDE-IV inhibitors has been solved in an obvious way.

Art. 33(3) PCT is also not fulfilled.

ad invention 2:

Claims which are not novel also do not fulfil Art. 33(3) PCT). For novel parts of the claims D1 would be the closest state of the art since D1 also deals with inhibitors of PDE-4. The problem to be solved is the provision of further compounds showing this activity. Since neither D1 nor D5 suggest compounds with cyclic substituents for R2, the solution is not obviously derivable from the prior art.

Novel parts of the claims fulfil Art. 33(3) PCT.

ad invention 3:

Closest state of the art is D1 since D1 also deals with inhibitors of PDE-4. The problem to be solved is the provision of further compounds showing this activity. Neither D1 nor D5 suggest compounds with thiazolidine or a dihydropyrazole rings as central unit. D13 discloses thiazolidine and pyrrole central units, but they are part of condensed systems. The proposed solution is thus not obviously derivable from the prior art.

Re Item VIII

Certain observations on the international application

The definition for R2 in claim 1 on page 65 line 60 appears to be erroneous (CH instead of

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/003893

CH2).